(12) EUROPEAN PATENT APPLICATION

(71) Applicant : Hewlett-Packard Company
3000 Hanover Street
Palo Alto, California 94304 (US)

(72) Inventor : Apffel, James A., Jr.
21317 Bertram Road
San Jose, California 95120 (US)
Inventor : Nordman, Robert G.
563 Lowell Avenue
Palo Alto, California 94301 (US)
Inventor : Martich, Mirko
2202-C3 Sherman Avenue
Evanston, Illinois 60201 (US)

(74) Representative : Williams, John Francis et al
WILLIAMS, POWELL & ASSOCIATES 34
Tavistock Street
London WC2E 7PB (GB)

(54) Method and apparatus for interfacing liquid chromatography-mass spectrometry systems.

(57) Close coupled momentum separator with integral removable source volume for particle beam liquid chromatography/mass spectrometry is provided. The inventive PB LC/MS system comprises a momentum separator (6) wherein the skimmers (20, 32) are designed to accommodate the particle beam conical dispersion so as to minimize the number of particles lost in the separator. In addition, the exit of the momentum separator is closely coupled to the entrance (38) of the MS source volume (60). The PB LC/MS system demonstrates improved linearity in signal and enhanced sensitivity.
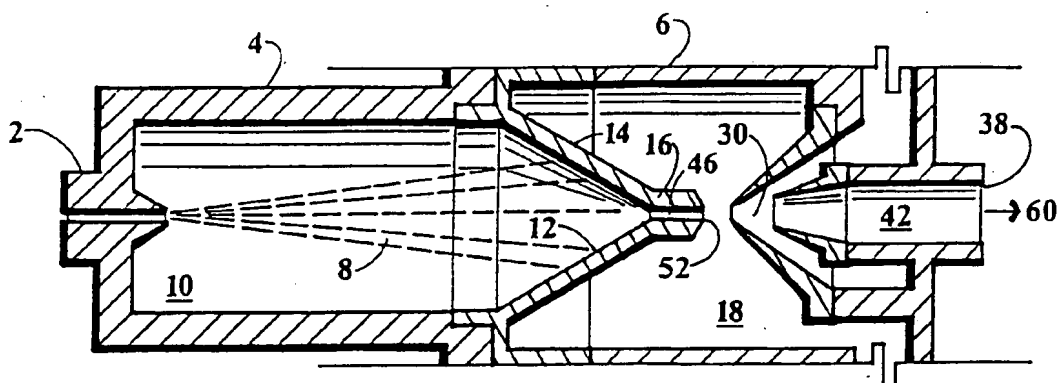
FIG._1.

EP 0 536 930 A1

Field of the Invention:

This invention relates generally to th introduction of samples into a mass spectrometry and more particularly to a method and interface device for separating desolvated particles from a stream of gas that are particularly suitable for use in combined liquid chromatography-mass spectrometry-systems.

Background of the Invention:

Particle beam liquid chromatography mass spectrometry (PB LC/MS) is a relatively new analytical technique. In prior art PB LC/MS systems, an aerosol consisting of helium dispersion gas and droplets containing relatively low levels of analyte dissolved in LC effluent is first generated by a nebulizer. The aerosol is injected into a heated desolvation chamber where the volatile components of the droplets (primarily HPLC effluent) are vaporized, resulting in a mixture of helium gas, solvent vapor, and desolvation solvent particles. This mixture then enters a two stage momentum separator in which the less massive components (such as solvent vapor and helium gas) are pumped away while the more massive particles continue through the system on, what was believed to be, a more or less straight line into the mass spectrometer source where the particles are vaporized, ionized, and mass analyzed. The momentum separator also serves as a pressure reduction and sample enrichment device, since most of the gas and solvent are pumped away, while most of the sample enters the mass spectrometer.

Browner et al., U.S. Patent No. 4,629,478, issued December 16, 1986, purports to describe a monodisperse aerosol generator which forms a stable jet of liquid at a velocity which allows columnar breakup into droplets of uniform size and spacing. Brandt et al., U.S. Patent No. 4,863,491, issued September 5, 1989, describes a multistage particle beam separator.

One problem encountered in the first generation of PB LC/MS instruments is poor linear response. Recent publications have shown that there is a systematic non-linearity in current instruments. See McLaughlin et al., "Particle Beam LC/MS for Drug Testing: Influence of Carrier Effect on Quantitation," paper 227, 6th (Montreux) Symposium on Liquid Chromatography/Mass Spectrometry; Behymer et al., "Liquid Chromatography/Particle Beam/Mass Spectrometry of Polar Components of Environmental Interest," Anal. Chem., 62, 1990, 1686-1690; and Bellar et al., "Investigation of Enhanced Ion Abundances from a Carrier Process in High Performance Liquid Chromatography Particle Beam Mass Spectrometry," J. Am. Soc. Mass Spectrom., 1, 1990, 92-98. Bellar and Behymer have r ferred to the probl m as a "carrier effect" because the phenomena can also be seen

as enhanced ion abundances in th presence of co-eluting components. This is the same as non-linearity, sinc non-linear b havior is a kind of self-carrier effect. These researchers have observed that by deliberately adding buffer to the mobile phase, a constant "co-eluting" component, the carrier effect is reduced and the linearity improves.

Summary of the Invention:

It is an object of the present invention to provide a more efficient and reliable PB LC/MS system with improved linearity in signal.

It is a further object of this invention to provide a compact PB LC/MS system with improved momentum separator transport efficiency and enhanced sensitivity.

It is a still further object of this invention to provide a PB LC/MS system wherein the source volume of the mass spectrometer is readily removable.

These and other objects are accomplished, in part, with the discovery that the "particle beam" emanating from the nozzle of the desolvation chamber is not a true collimated beam as previously assumed. Rather, the particles form an inhomogeneous conical dispersion or spread of particles with the largest ones concentrated near the center. The present invention comprises a PB LC/MS system wherein the skimmers of the momentum separator are designed to accommodate the conical dispersion so as to minimize the number of particles lost in the separator. In addition, in the inventive PB LC/MS devices, the exit of the momentum separator is very closely coupled to the entrance of the MS source volume. In one aspect of the invention, the exit of the second skimmer of the momentum separator and the entrance of the source volume can be the same orifice, although even a modestly close coupled system results in markedly improved linear response.

In another aspect of the invention, the momentum separator and source entrance are constructed as an unit so that the surfaces of the source volume, including the repeller and draw out lens, come into contact with samples or solvents. The source volume can be easily withdrawn from the MS vacuum system without venting the vacuum to atmosphere. The source volume can then cleaned and/or replaced. Different source volume designs can be readily interchanged for optimal conditions for Electron Impact (EI) or Chemical Ionization (CI) operation.

Brief Description of the Drawings:

Figure 1 is a cross-sectional view of a particle beam interface.

Figure 2 is a cross-sectional view of the skimmers of a momentum separator.

Figure 3 is a cross-sectinnal vi w of a momentum

separator.

Figure 4 is a cross-sectional vi w of a schematic of an interfac that is clos coupled to the source volume of a mass spectrometer.

Figure 5 is a cross-sectional view of a schematic of an interface that is close coupled to the source volume of a mass spectrometer.

Figure 6 is a cross-sectional view of a schematic of an interface with a gate valve.

Figure 7 is a graph of signal versus gate valve position.

Detailed Description of the Invention:

Hitherto it was believed that with the PB LC/MS technique, the "particle beam" which resulted from the supersonic jet expansion in the initial nozzle section of the momentum separator was a substantially perfectly collimated beam of monodispersed droplets. See Willoughby and Browner, "Monodisperse Aerosol Generation Interface for Combining Liquid Chromatography with Mass Spectrometry," Anal. Chem., S, 1984, 2626-2631. Experiments with the present invention establish that the above assumption is incorrect.

It is believed that nonlinear behavior in prior art PB LC/MS systems is, in part, the result of particle size discrimination by the momentum separator. This discrimination occurs even if it is assumed that the aerosol entering the desolvation chamber is "monodispersed", that is, all droplets are precisely the same size. The reason is that when analytes are introduced into the system at different concentrations, the particles derived from desolvated monodispersed droplets with varying analyte concentrations will be polydispersed. A momentum separator (which is a vacuum system) has a practical size cut-off level so that small particles are subject to removal. This is particularly the case when the analyte concentration is low.

The following calculations show how the particle size will vary with sample concentration.

(1) Particle Mass:

$$Weight(W_p) = \frac{\pi}{6}D^3_{droplet} \times Concentration(C)$$

(2) Particle Volume (assuming that particle density is equal to bulk density):

$$V_{particle} = \frac{W_p}{\rho_p}$$

(3) Particle Diameter:

$$d_p = \sqrt[3]{\frac{6V_p}{\text{II}}}$$

$$d_p = \sqrt[3]{\frac{6W_p}{\rho_p \text{II}}}$$

$$d_p = D_{droplet}\sqrt[3]{\frac{C}{\rho_p}}$$

For the above equations, W_p is the particle weight, $D_{droplet}$ is the droplet diamet r, $V_{particle}$ is the

particle volum , ρ_p is the particle d nsity, and D_p is the particle diameter.

As is apparent, th particle diameter is directly proportional to the droplet diameter and the particle diameter is proportional to the cube root of the concentration. It is expected that the supersonic jet generated at the momentum separator nozzle will have larger particles near the axis with smaller particles on the outside. In addition, as the particle size decreases, the "particle beam" will spread out even more.

The actual phenomenon which results in this cutoff level may involve the skimmers in the momentum separator or it may involve the fact that the particle beam itself has a small but finite divergence angle which results in a conical spread of particles inhomogeneous in particle size, that is, the larger particles are concentrated in the center, while the small particles are on the periphery. If the particle beam is required to transmit particles over a distance, the outside smaller particles can be lost against the transfer conduit walls. Thus, at lower levels, there would be a lower than expected response.

Referring to Fig. 1, a cross-sectional view of the particle beam interface of this invention is shown. This system comprises nebulizer 2 where the liquid solution is broken into droplets, desolvation chamber 4 where the solvent is evaporated, leaving particles which might contain traces of residual solvent, and momentum separator 6 where the particles are further desolvated and separated from solvent vapors, in preparation for ionization. The nebulizer 2 projects a stream of solvent droplets 8 into a cylindrical chamber 10. Here the solvent is evaporated, leaving an aerosol or suspension of particles containing a small proportion of residual solvent.

The mixture of solvent vapors, gases and desolvated particles is collected by the tapered collector side 12 of the nozzle plate 14 and, by means of the pressure drop across the nozzle, is projected through the nozzle 16 as a supersonic jet. The nozzle passageway 46 has inner diameter (d_n) and outlet 52. The higher mass particles tend to concentrate near the center of the axis of the jet with the lower mass gas molecules further from the axis, thus forming a "particle beam." As shown in Fig. 2, the "particle beam" in actuality comprises an inhomogeneous conical dispersion or spread 51 of particles with the largest ones concentrated at its center along central axis 50. The angle of dispersion and the distribution of particles within the dispersion will vary.

The gas and particle mixture is passed through a series of chambers in the momentum separator of this invention, each chamber having a stronger vacuum than the preceeding chamber. The term "downstream", as us d herein, is defined to mean the direction of material flow from weaker vacuum to stronger vacuum. The particles (or dispersion) travel into and through the first stag chamber 18 of the momentum

separator 6 where more of the solvent vapors and other gases are removed from the mixture. The first stage skimmer 20 has a central axial opening or aperture 22 of sufficient diameter (d_{s1}) so that the conical dispersion 51 is not deflected by the skimmer. The gases are deflected by the conical surface 24 of the first skimmer 20.

Upon exiting the first stage chamber, the dispersion enters into the second stage chamber 30 where the gases are further expanded and separated from the particles. The dispersion 51 continues to travel through the axial, central opening 34 of the second skimmer 32. The gases are deflected by the conical surface 36 of the second skimmer 32. Orifice 34 is of sufficient diameter (d_{s2}) so that the conical dispersion 51 is not deflected by the skimmer. Thereafter, the dispersion traverses a short passageway or transfer tube 42 before entering the source volume of a mass spectrometer. In this close coupled configuration as shown in Fig. 1, the transfer tube is relatively wide and short so that the dispersion does not come into contact with the walls of the tube. Moreover, the entrance 38 of the source volume 60 is also wide enough to "capture" the entire dispersion.

Referring to Fig. 3, the separation distances between the nozzle outlet 52 and aperture 22, aperture 22 and aperture 34, and aperture 34 and the entrance 38 of the transfer tube are designated d_{ns}, d_{ss}, and d_{st}, respectively. The transfer tube has a diameter d_{s3} and a length d_t; and the entrance of the source volume 60 has a diameter d_{source}. As is apparent, $d_n < d_{s1} < d_{s2} < d_{s3}$. In the embodiment shown in Fig. 3, the transfer tube is not attached to the entrance of the source volume of the mass spectrometer. In the close couple system of Fig. 1, the transfer tube is attached to the entrance. In another close coupled embodiment described below, the transfer tube can be effectively eliminated altogether.

In the design of prior art PB LC/MS systems, because the "particle beam" was considered more or less a collimate beam, the skimmers and source entrance were not adequately constructed to take into consideration the conical dispersion of particles. The loss of particles in the momentum separator and in the transfer tube contributed to the non-linear response in prior art systems. Specifically, in prior art designs, the diameters of the skimmer apertures were often too small (or either d_{ns}, d_{ss}, or d_{st} was too long) to accommodate dispersion. Moreover, the transfer tube between the momentum separator and the relatively small diameter source volume entrance aperture further contributed to the problem. The result was that with prior art PB LC/MS systems, small particles are lost due to deflection by the skimmers, impact with the transfer tube walls, and blockage by the small source entrance.

The inventive PB LC/MS employs a momentum separator wherein the skimmers are configured so that the size of each aperture is large enough to encompass the periphery of the dispersion cone. In addition, the exit of the second skimmer can be closely coupled to the mass spectrometer source entrance. This minimizes the diameter of the dispersion cone section at the source entrance thereby allowing a maximum proportion of smaller particles to enter the source. As is apparent, the skimmer aperture and source entrance diameters are arranged in increasing proportions so that the largest proportion of the dispersion cone can be included. However, this requires that the vacuum system and liquid solution flow rate be adjusted so that the increasing orifice size does not result in too high a source pressure.

Another embodiment of the inventive device with close coupling, shown schematically in Fig. 4, comprises a desolvation chamber 61 with nozzle 62, and a momentum separator. Source volume 60 is an integral part of the momentum separator, which includes skimmers 63 and 64. This configuration allows the entire source volume to be removed through a vacuum port. The source volume includes hot target 65, filament 66, and repeller and entrance lens (collectively, 68 in plane). The ions are directed to target 67. In this embodiment, the second skimmer 64 could be an orifice in the source wall. The skimmer orifice and source entrance diameters are arranged in increasing proportions so that the largest proportion of the dispersal cone is included.

The device in Fig. 5 is similar to the embodiment of Fig. 4 and comprises desolvation chamber 71 with nozzle 72 and a momentum separator that includes skimmers 73 and 74. Gases are pumped out from the second stage chamber through opening 79. However, as is apparent, the source volume 70 is different with regard to some of its internal structures, namely: entrance lens 75, repeller 76, electrical connection for repeller 77, and ski-like contact 78.

With the present invention, close coupling results in improved linear response, but source fouling remains a problem. PB LC/MS, especially systems employing chemical ionization with methane, results in rapid source performance deterioration due to fouling of the source. Furthermore, use of non-volatile particles (e.g., buffers) aggravates the fouling. The embodiments as shown in Figs. 4 and 5 permits the entire source volume to be conveniently removed for replacement or cleaning.

In the above embodiments, each device comprised a momentum separator that had two vacuum chambers. However, momentum separators with only one vacuum chamber or with three or more vacuum chambers can also be employed. In each vacuum chamber, the skimmer orifice must be of sufficient construction to accommodate the dispersion cone. Finally, the momentum separator should be closely coupled to the source assembly entrance.

As stated previously, one aspect of the present

invention is the discovery that th "particle beam" emanating from the initial nozzl of the momentum separator is not a true collimated b am. To confirm this, a gate valve was positioned between the second skimmer and the source entrance of a mass spectr-ometer to show the expansion angle of the particle beam.

For this experiment, a standard Hewlett-Packard (Palo Alto, California) HP5989 Particle Beam LC/MS in which the isolation valve between the particle beam interface and the mass spectrometer vacuum manifold was replaced with a 10 mm wide VAT gate valve. Except for the presence of the gate valve, the instrument was operated in a standard fashion. Sam-ples (cortisol in methanol) were injected into a mobile phase of methanol at 0.4 ml/min in a Flow Injection Analysis (FIA) mode (i.e., no chromatography column present). A HP1090 HPLC was used to deliver the liq-uid flows and to make 1 μl sample injections at differ-ent concentrations. The particle beam nebulizer was adjusted to optimize the signal in a normal way. The helium flow was approximately 2 L/min and the neb-ulizer fused silica capillary was adjusted to slightly ex-tend past the nebulizer capillary. The desolvation chamber was at approximately 45° C. Fig. 6 shows the axial measurements for the system wherein the particle beam enters aperture 80 of the second skim-mer 81 and exits at aperture 82. Dispersion cone 85 is formed about central axis 86. As depicted, the source entrance cone 84 blocks some of the particles of the dispersion cone from entering mass spectrome-try source volume 86. The position of gate valve 83 ranged from 0 (fully opened) to 15 (closed).

Fig. 7 shows the effect of closing the gate valve on the signal for samples at different concentrations ranging from approximately 7.81 to 1000 ng/ml. Curves 701, 702, 703, 704, 705, 706, 707 and 708 correspond to 7.51, 15.62, 31.25, 62.5, 125, 250, 500 and 1000 ng/ml respectively. The y axis is the signal height, the x axis is the position of the gate valve. "Height" refers to the peak height in arbitrary signal counts of a peak profile corresponding to an injected sample probe.

As is apparent, by closing the gate valve, the sig-nal was attenuated as the gate passed the expansion cone of the particle beam. Indeed, the amount of clo-sure required for the effect to set in comports with data regarding the conical solid angle which was ulti-mately determined by what can pass through the or-ifice in the source.

The gate valve experiment was repeated with a Particle Beam LC/MS system entitled the "pretty close coupled 5989" prototype in which the mass spectrom ter source is brought closer to the particle beam interface. A standard HP5989 PB LC/MS was used but with all connection valving between the par-ticle beam interface and the mass spectrom ter source removed. The particle beam int rface was re-

placed with a prototype in which the standard skim-mers were mounted as close to the mass spectrom-ter vacuum manifold wall as possible. This had the ffect of making this prototyp approximately 15 cm closer coupled than the standard system.

With this "pretty close coupled" system, it was found that the cut-off is sharper which indicates that the expansion cone solid angle is intercepted closer to its vertex at the exit of the second skimmer.

Claims

1. A liquid chromatography-mass spectrometry par-ticle separator comprising:
   a vacuum chamber (18);
   means for introducing a mixture of gas and particles into said vacuum chamber with said particles forming a conical dispersion upon enter-ing said chamber;
   a skimmer (20) having an aperture (22) of sufficient construction so that approximately the entire conical dispersion travels through said aperture; and
   a mass spectrometer downstream of said skimmer and having a source assembly (60) with an entrance (38), said aperture being closely cou-pled to said source assembly entrance.

2. The liquid chromatography-mass spectrometry particle separator as defined in claim 1 wherein said skimmer comprises a conical surface (24) which radially narrows to an apex opposed to said introduction means with said skimmer aperture in said apex.

3. The liquid chromatography-mass spectrometry particle separator as defined in claim 2 wherein said source assembly entrance (38) is of suffi-cient construction so that approximately the en-tire conical dispersion travels through said source assembly entrance.

4. The liquid chromatography-mass spectrometry particle separator as defined in claim 3 wherein said aperture (22) is attached to said source as-sembly entrance (38).

5. The liquid chromatography-mass spectrometry particle separator as defined in claim 4 wherein said source assembly (60) is removable.

6. A liquid chromatography-mass spectrometry par-ticle separator comprising:
   a first vacuum chamber (18);
   means for introducing a mixture of gas and particles into said first vacuum chamber, said particles forming a conical dispersion upon enter-

ing said first chamb r;

a first skimmer (20) having a first aperture (22) of sufficient construction so that approximately the entir conical dispersion travels through said first aperture;   5

a second vacuum chamber (30) downstream of and communicating with said first aperture;

a second skimmer (32) having a second aperture (34) of sufficient construction so that   10 approximately the entire conical dispersion travels through said second aperture; and

a mass spectrometer downstream of said second skimmer and having a source assembly (60) with an entrance (38), said second aperture   15 being closely coupled to said source assembly entrance.

7. The liquid chromatography-mass spectrometry particle separator as defined in claim 6 wherein   20 said first skimmer (20) comprises a first conical surface (24) which radially narrows to a first apex opposed to said introduction means and wherein said second skimmer (32) comprises a second conical surface (36) which radially narrows to a   25 second apex opposed to said introduction means, said second skimmer being downstream of said second vacuum chamber (30) so that said conical dispersion exits said second vacuum chamber through said second aperture (34).   30

8. The liquid chromatography-mass spectrometry particle separator as defined in claim 7 wherein said source assembly entrance (38) is of sufficient construction so that approximately (he en-   35 tire conical dispersion travels through said source assemhly entrance.

9. The particle separator as defined in claim 8 wherein said second aperture (34) is attached to   40 said source assembly entrance (38).

10. The particle separator as defined in claim 9 wherein said source assembly (60) is removable.
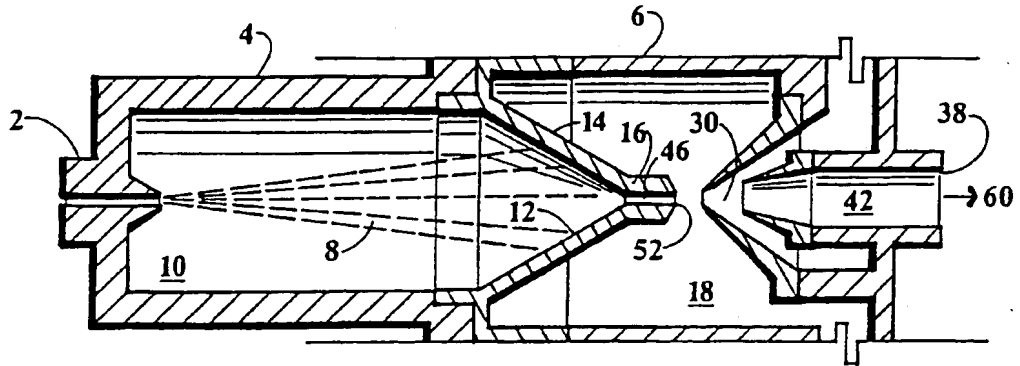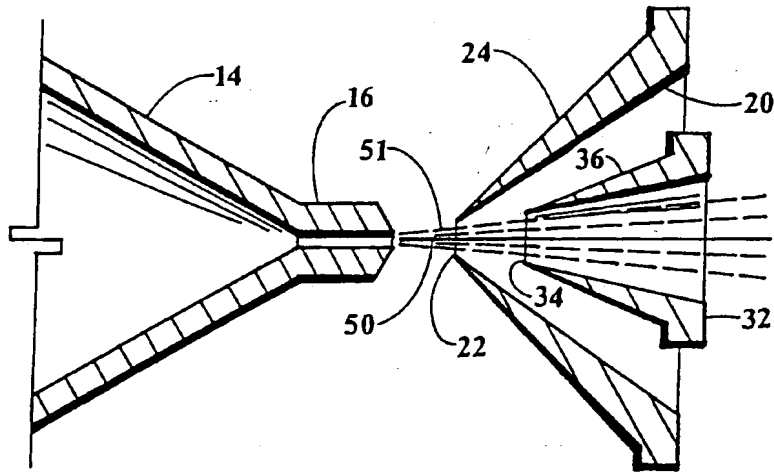
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FIG._1.

FIG._2.
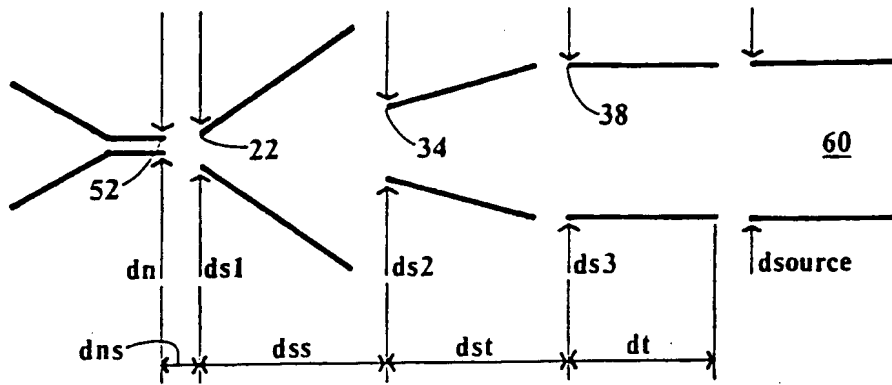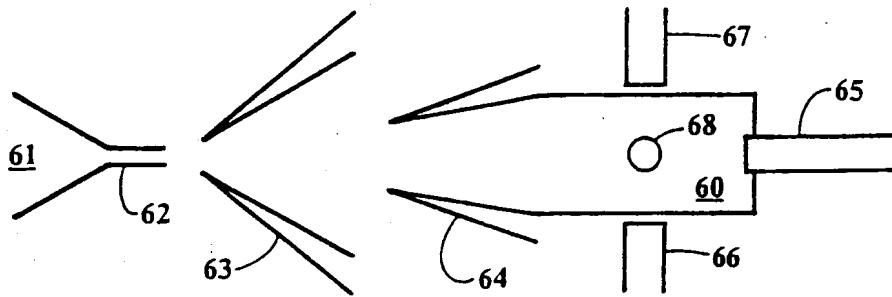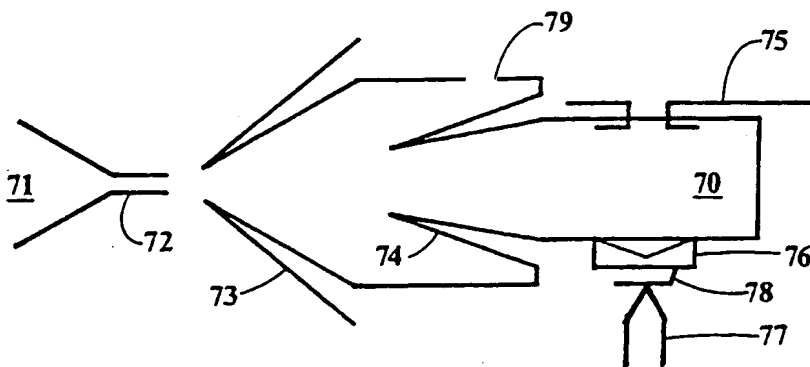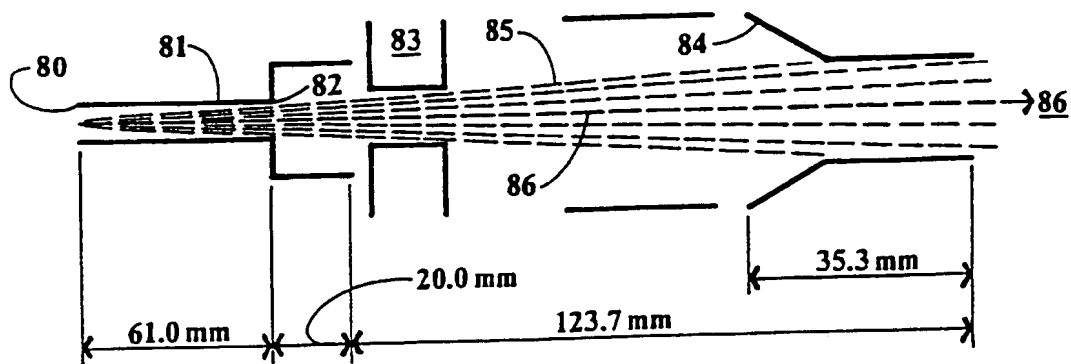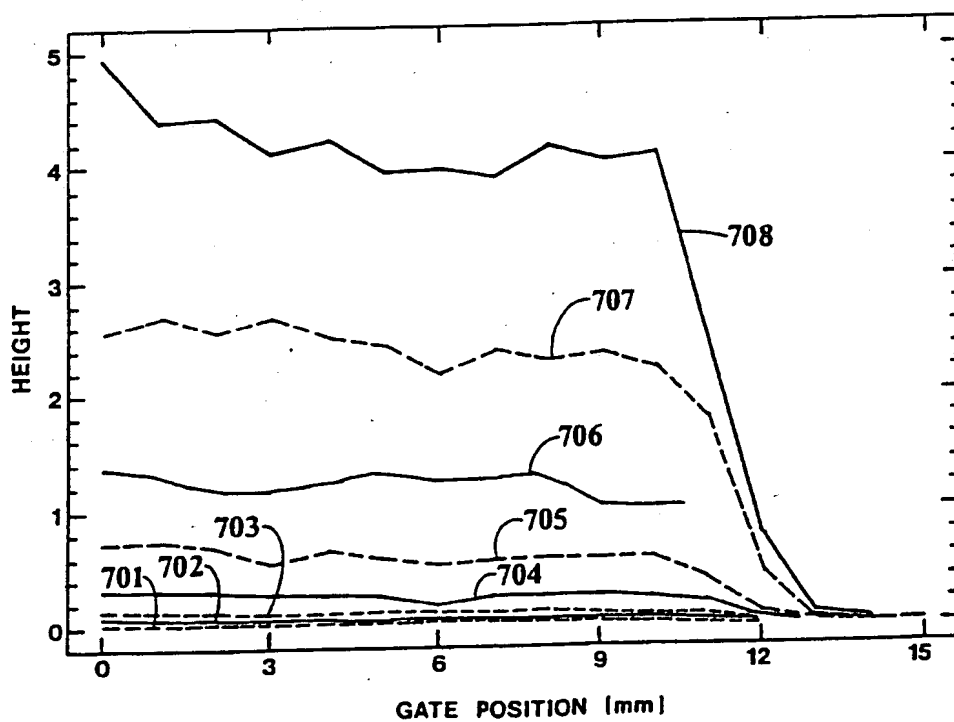
FIG._3.

FIG._4.

FIG._5.

FIG._6.

FIG._7.

European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 8879

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-4 358 302 (DAHNEKE) * column 3, line 33 - column 5, line 19; figure 1 * * column 7, line 4 - line 28 * * column 8, line 11 - column 9, line 54; figure 3 * ---	1,2	G01N30/72 H01J49/04
D,A	EP-A-0 343 972 (HEWLETT-PACKARD) * column 5, line 41 - line 63; figure 4 * ---	1,6	
A	REVIEW OF SCIENTIFIC INSTRUMENTS vol. 52, no. 9, September 1981, NEW YORK US pages 1283 - 95 RANDALL ET AL. * page 1284, column 2, paragraph 2 - page 1285 * * page 1287, column 2, paragraph 3 - page 1288, column 1 * -----	1,6	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) G01N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 NOVEMBER 1992	ZINNGREBE U.

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